Clinical Characteristics and Medication Use among Premenopausal Women with Osteoporosis and Low BMD: The Experience of an Osteoporosis Referral Center

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Abstract

Aims: Osteoporosis is uncommon in premenopausal women, and most cases have a secondary cause. Women with osteoporosis and no known secondary cause are said to have idiopathic osteoporosis (IOP). We aimed to estimate the proportion of premenopausal women seen in our referral center with IOP as opposed to secondary osteoporosis, to describe their clinical characteristics, to compare women with a low-trauma fracture history with those with low bone mineral density (BMD) alone, and to estimate the frequency of bisphosphonate use.

Methods: We reviewed medical records from all premenopausal women evaluated for osteoporosis or low BMD in our center during 2005. We included premenopausal women diagnosed on the basis of low-trauma fracture, low BMD or both (Z score ≤ -2.0 or T score ≤ -2.5), or both.

Results: Among these patients ($n = 61$; mean age 37 ± 8), 57 (93%) were Caucasian, 34 (57%) had a family history of osteoporosis, and 26 (43%) had used bisphosphonates. The most common secondary causes were amenorrhea (34%, $n = 21$), anorexia nervosa (16%, $n = 10$), and glucocorticoid exposure (13%, $n = 8$). After exclusion of secondary causes, 39% (24 of 61) of the entire group and 48% (14 of 29) of the fracture group were thought to have IOP. Women with a known secondary cause had lower BMD Z scores at the spine and hip than those with IOP. Women with low BMD and no fractures had shorter stature and weighed less than those with fractures, but overall differences between the groups were not statistically significant. Bisphosphonates had been prescribed for 38% (11 of 29) of women with a fracture history and 47% (15 of 32) of women with low BMD and no fractures.

Conclusions: Our findings suggest that IOP is common among premenopausal women with osteoporosis or low BMD evaluated at a referral center. The smaller stature of women diagnosed only on the basis of BMD criteria raises the question of whether their areal BMD measurements are spuriously low because of smaller bone size. The high proportion of premenopausal women who had been prescribed oral bisphosphonates for low BMD measurements is of concern, as such women are likely to be at low short-term risk of fracture, and a more conservative approach to therapy is preferable in this group.

Introduction

OSTEOPOROSIS IS GENERALLY UNCOMMON in premenopausal women. Moreover, most premenopausal women with osteoporosis have a medical condition or drug exposure that has either interfered with attainment of optimal peak bone mass or caused premature bone loss. The disorders most commonly associated with osteoporosis in young women include premenopausal estrogen deficiency, anorexia nervosa,

celiac disease, and exposure to drugs that cause bone loss, particularly glucocorticoids.^{1–3} Young women with osteoporosis, in whom secondary causes have been excluded by history, physical examination, and a detailed biochemical evaluation, are considered to have idiopathic osteoporosis (IOP).

There is considerable controversy about the diagnosis of osteoporosis in premenopausal women.^{4–6} Some experts believe that it is inappropriate to base the diagnosis of osteo-

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porosis on bone mineral density (BMD) criteria alone in premenopausal women and consider that a history of low-trauma fracture or a known secondary cause of osteoporosis should be required. It is also unclear which bone density criteria should be used to characterize BMD measurements in premenopausal women.^{4,6} The World Health Organization (WHO) criterion for diagnosis of osteoporosis by BMD measurement is a T score of -2.5 or less at the spine, hip, or forearm.⁷ A T score is the number of standard deviations (SD) by which a patient's BMD deviates from peak bone mass of a young normal population (aged 25–35) of the same race and gender. However, the WHO diagnostic criteria for osteoporosis and osteopenia were derived from studies of postmenopausal Caucasian women^{7,8} and should not be used to categorize BMD measurements in young women because they are at much lower risk of fracture. Instead, the International Society for Clinical Densitometry (ISCD) recommends using the Z score, or the number of SDs by which a patient's BMD deviates from a population of the same age, race, and gender to characterize bone mass measurements in premenopausal women.⁸ In addition, the ISCD recommends avoiding such terms as osteoporosis and osteopenia when reporting BMD measurements in young women and suggests that young women with BMD Z scores < -2.0 should be categorized as having low BMD or BMD that is below expected range for age, and those with Z scores > -2.0 should be categorized as having BMD that is within the expected range for age.

The management of young women with low BMD measurements or low-trauma fractures is also uncertain. Currently available drugs to treat osteoporosis are generally not approved for use in women of childbearing potential, the only exceptions being oral alendronate and risidronate for prevention and treatment of glucocorticoid-induced osteoporosis. It has been our clinical experience, however, that many otherwise healthy, premenopausal women are offered bisphosphonates for treatment of low BMD measurements even if they have not sustained fractures.

In this study, we aimed to estimate the proportion of premenopausal women seen in our tertiary care medical center with IOP as opposed to secondary osteoporosis or low BMD, to describe the demographic, anthropometric, densitometric, and reproductive characteristics and vitamin D status of young women with osteoporosis or low BMD, and to determine if women with a history of fracture differed from women diagnosed solely on the basis of low BMD. In addition, we wished to estimate the frequency with which premenopausal women were prescribed bisphosphonates and if that frequency differed according to whether or not the women had sustained fractures.

Materials and Methods

We conducted a retrospective review of medical records from all women ≤ 50 years of age who had an initial visit with any physician in our Metabolic Bone Diseases Program (MBDP) at Columbia University Medical Center (CUMC) between January 1 and December 31, 2005, and who had received a diagnosis of osteoporosis, osteopenia, or fracture. We excluded women who were postmenopausal, defined as amenorrhea for at least 6 months or serum follicle-stimulating hormone (FSH) >20 IU/L.

Cases were defined based on BMD or low-trauma fracture criteria. BMD measurements were obtained by dual energy x-ray absorptiometry (DXA). Women were included on the basis of low BMD if they had a Z score (comparison to an age-matched reference database) ≤ -2.0 or T score (comparison to young normals) ≤ -2.5 at one or more sites (lumbar spine, total hip, femoral neck, distal radius). Because some women included on the basis of low BMD had no fractures and no known secondary cause and, thus, would not meet the current ISCD definition of "osteoporosis" for premenopausal women, we use the term "osteoporosis or low BMD" to refer to the cases as a whole.

Women were included on the basis of low-trauma fracture if they had sustained a fracture at age ≥ 18 as a result of trauma equivalent to a fall from standing height or less, regardless of BMD; fractures of the skull and digits were excluded. As some women meeting the BMD inclusion criteria had also sustained both high- and low-trauma fractures, overall cases were categorized as "low BMD" when case status had been determined based on BMD criteria alone, with no history of fracture, whereas "fracture cases" were those who had sustained any fracture (excluding skull and digits) after the age of 18, whether or not they also had low BMD.

For all patients evaluated at the MBDP, a detailed standardized questionnaire is completed by the evaluating physician at the time of the initial visit. Premenopausal women with osteoporosis or low BMD are evaluated for secondary causes of bone loss, including amenorrhea, eating disorders, hyperthyroidism, hyperparathyroidism, Cushing's syndrome, hypercalciuria, calcium and vitamin D deficiency, celiac disease, autoimmune and inflammatory conditions, alcoholism, renal disease, liver disease, osteogenesis imperfecta, and drug exposures (glucocorticoids, immunosuppressants, antiseizure medications, heparin, chemotherapy). We extracted data on age, date of birth, race/ethnicity, menarchal age, reproductive and lactation history, family history of osteoporosis, current or previous use of osteoporosis medication, calcium and vitamin D supplementation, history of known secondary causes for osteoporosis, alcohol and tobacco use, and fracture history (sites, age at fracture, degree of trauma). BMD, height, and weight are also obtained at the initial visit. Serum 25(OH) vitamin D (25D) measurements were made on convenience samples by radioimmunoassay (RIA) in a commercial laboratory.

Estimates of means, prevalences, and variance were obtained for each of the clinical characteristics of premenopausal women with osteoporosis or low BMD. For overall comparisons among the four groups (Table 3), comparisons were based on ANOVA models for continuous variables and Fisher's exact test for categorical variables. A *p* value of <0.05 was considered to indicate statistical significance.

Results

Of 389 new patients evaluated at the MBDP at CUMC during 2005, 61 were premenopausal women, of whom 29 (48%) had a history of fracture. They were predominantly Caucasian (93%) and in their mid-30s (mean age 37 ± 8 years). Mean serum 25D was 33 ± 15 ng/mL. The majority of the women had a family history of osteoporosis (57%, 34 of 61) and were taking calcium and vitamin D supplements at the time of their initial evaluation (82%, 50 of 61, and 70%, 43 of

61, respectively). Forty-three percent (26 patients) had a history of current or past treatment with bisphosphonates.

A secondary cause of osteoporosis (Table 1) was present in 37 women (61%). The most common secondary causes were a history of amenorrhea of >6 months duration, anorexia nervosa, steroid exposure, and celiac disease (based on serologic studies). Other secondary causes (drugs associated with bone loss, thyrotoxicosis, hyperparathyroidism, and rheumatologic diseases) accounted for the remaining patients. After exclusion of secondary causes, 24 women were considered to have idiopathic osteoporosis or idiopathic low BMD (IOP). Women with IOP accounted for 39% (24 of 61) of the whole group and 48% (14 of 29) of those with a history of fracture.

Twenty-nine women (48%) had a history of fracture, 58% (14 of 24) among those with IOP and 41% (15 of 37) among those with a secondary cause. Five women had sustained vertebral fractures, 4 had sustained hip fractures, and 3 had pelvic fractures (Table 2). Of those with a history of fractures, 52% (15 of 29) had sustained multiple fractures, and 28% (8 of 29) had BMD T scores > -2.5 and BMD Z scores > -2.0 at all sites.

We divided the 61 women into four mutually exclusive groups (positive fracture history with and without a known secondary cause and negative fracture history with and without a known secondary cause). Their clinical characteristics are shown in Table 3. Based on models examining overall differences between the groups, differences were significant for age, menarchal age, parity, and BMD Z scores at the spine and hip. Menarchal age was highest in those with a known secondary cause of osteoporosis and a history of fractures. Those with low BMD, no known secondary cause, and no fracture history had the highest mean age and parity. ANOVA models showed significant between-groups differences in lumbar spine, total hip, and femoral neck BMD Z scores. Between-groups comparisons (Student's *t* tests) showed that those with a known secondary cause had a significantly lower mean spine BMD Z score than those with IOP (-2.39 ± 0.84 vs. -1.58 ± 0.96 , $p = 0.001$).

Although mean heights and weights were lowest in those with low BMD and no history of fracture, heights and weights were quite variable, and the overall difference between the groups was not statistically significant. Among those with fractures and those with low BMD and no fractures, 6 women in each group had a body mass index (BMI) <18.5 kg/m².

Serum 25D levels were available in 56 patients. The groups did not differ with respect to serum 25D levels, which were >30 ng/mL on average and >15 ng/mL in all patients. Nine women in the fracture group (35%) and 17 women in the low BMD group (57%) had 25D levels between 15 and 29 ng/mL, in the insufficient range. The groups were also similar with respect to a family history of osteoporosis, glucocorticoid exposure, and use of calcium and vitamin D supplements at the time of their evaluation.

Some patients in all groups had a history of current or prior bisphosphonate treatment. Bisphosphonates had been used by 50% (12 of 24) of those with IOP and 38% (14 of 37) of those with secondary causes. Secondary causes diagnosed in those treated with bisphosphonates included anorexia nervosa (4 patients), celiac disease (2 patients), and glucocorticoid use (4 patients). Bisphosphonates had been used by 47% (15 of 32) of those with low BMD and no history of fracture and by 38% (11 of 29) of those who had sustained fractures.

Discussion

This retrospective record review identified 61 premenopausal women with osteoporosis or low BMD who were evaluated at a tertiary referral center over a 1-year period. Case definition for this study was based on either a history of low-trauma fractures or very low BMD measurements. The majority (61%) had a secondary cause of osteoporosis, the most common being premenopausal amenorrhea, anorexia nervosa, glucocorticoid exposure, and celiac disease. As no secondary cause could be identified in 39%

TABLE 1. SECONDARY CAUSES OF OSTEOPOROSIS FOUND

<i>Secondary cause</i>	<i>Number affected</i>	<i>% of total (n = 61)^a</i>
Idiopathic—no cause found	24	39
History of amenorrhea > 6 months	21	34
Anorexia nervosa	10	
Depot medroxyprogesterone acetate	2	
Medications to suppress pituitary function	1	
Glucocorticoid exposure	8	13
Rheumatologic disease	3	
Organ transplant (liver, lung, kidney)	3	
Celiac disease (based on serologic study)	6	10
Medications to suppress pituitary function (<6 months)	1	2
Hyperparathyroidism	3	5
Seizure medication use	2	3
Hyperthyroidism	1	2
Hereditary exostosis	1	2

^aPercent of total is >100%. Many women had more than one secondary cause (e.g., some women with celiac disease or glucocorticoid exposure also had amenorrhea).

TABLE 2. FRACTURES SUSTAINED

Fracture type	Number of women	% of total with fractures (n = 29) ^a
Vertebral	5	17
Rib	2	7
Hip	4	14
Pelvic	3	10
Forearm	8	28
Elbow	2	7
Tibia, ankle, foot	13	45

^aNote that 52% of women had sustained multiple fractures.

of the group as a whole and 48% of those with a history of fractures, our results suggest that IOP is common in premenopausal women referred to a tertiary care center for evaluation of osteoporosis. The high number of premenopausal women reporting a fracture history and the high prevalence of current or past bisphosphonate use are both noteworthy observations in this population.

These findings confirm and extend our previous analysis of 111 women <55 years of age evaluated for osteoporosis or low bone mass at our center between 1990 and 1997.³ Of

the 45 premenopausal women in that analysis, 24 (53%) had a secondary cause of bone loss, whereas in 21 (47%), no contributing etiology could be identified, slightly higher than in this study in which the proportion with IOP was 38%. The majority of patients in both studies reported a family history of fracture. In contrast to the results of this study, in which premenopausal estrogen deficiency was by far the most common secondary etiology, glucocorticoid therapy was the most frequent cause of osteoporosis in our first study. Our findings are also consistent with a report by Peris et al.⁹ of 52 premenopausal women referred to a Spanish tertiary care rheumatology center for evaluation of osteoporosis; 44% of their patients had an identifiable secondary cause, the most common being Cushing's syndrome and pregnancy-associated osteoporosis (not considered a secondary cause in our study), and 56% were considered to have IOP.

In our study, there were several interesting differences between groups of women categorized according to fracture history and whether or not a known secondary cause was present (Table 3). Menarchal age was highest in those with a fracture history and a known secondary cause of osteoporosis. The illnesses or medications that defined their secondary cause status may also have been associated with later onset of menses. The highest mean age and parity were

TABLE 3. COMPARISON OF SUBJECTS WITH AND WITHOUT A HISTORY OF FRACTURES AND WITH AND WITHOUT A KNOWN SECONDARY CAUSE

	History of fracture		No history of fracture		p ^a
	Known secondary cause n = 15 Mean ± SD	IOP n = 14 Mean ± SD	Known secondary cause n = 22 Mean ± SD	IOP n = 10 Mean ± SD	
Race: % Caucasian	100%	93%	91%	90%	NS
Age (years)	37 ± 8	37 ± 7	33 ± 8	45 ± 4	0.001
Height (cm)	165.3 ± 5.8	161.5 ± 7.4	159.1 ± 9.8	159.8 ± 5.1	NS
Weight (kg)	56.5 ± 8.5	55.5 ± 10.7	53.9 ± 13.7	49.5 ± 7.3	NS
BMI (kg/m ²)	20.7 ± 3.0	21.6 ± 2.1	21.1 ± 4.4	19.4 ± 2.7	NS
Menarchal age (years)	14.5 ± 1.9	13.0 ± 1.3	13.1 ± 1.4	13.8 ± 1.8	0.03
Parity (no. of live births)	0.7 ± 1.2	0.9 ± 1.1	0.5 ± 1.4	2.6 ± 3.1	0.02
Family history of osteoporosis (%)	60%	64%	48%	60%	NS
Calcium supplement use (%)	87%	86%	73%	90%	NS
Vitamin D supplements (%)	64%	93%	62%	80%	NS
Oral bisphosphonates, current or past (%)	33%	43%	41%	60%	NS
Serum 25(OH) vitamin D (ng/mL)	31 ± 9	36 ± 9	34 ± 23	30 ± 6	NS
Mean BMD Z score					
Lumbar spine	-2.11 ± 0.99	-1.61 ± 1.11	-2.61 ± 0.65	-1.54 ± 0.80	0.006
Total hip	-0.98 ± 0.96	-1.62 ± 0.76	-2.00 ± 0.61	-1.29 ± 0.74	0.005
Femoral neck	-1.29 ± 0.83	-1.60 ± 0.66	-1.94 ± 0.67	-1.17 ± 0.81	0.03
Distal radius	0.03 ± 0.87	-0.14 ± 1.06	-0.91 ± 1.03	-0.72 ± 1.28	NS
Mean BMD T score					
Lumbar spine	-2.33 ± 0.93	-1.85 ± 0.96	-2.61 ± 0.69	-2.27 ± 0.66	NS
Total hip	-1.35 ± 1.07	-1.89 ± 0.79	-2.11 ± 0.54	-1.83 ± 0.60	NS
Femoral neck	-1.69 ± 0.88	-1.90 ± 0.70	-2.06 ± 0.53	-1.86 ± 0.75	NS
Distal radius	-0.16 ± 0.84	-0.65 ± 1.30	-1.01 ± 1.01	-1.03 ± 1.05	NS

^aOverall differences among the four groups: comparisons based on ANOVA models for continuous variables and Fisher's exact test for categorical variables.

found among those with no fracture history and no known secondary cause. It is likely that their older age accounts for their higher parity. Their older age may reflect referral patterns, in that premenopausal women without fractures and without an obvious secondary cause of osteoporosis may take longer to come to medical attention. In contrast, women with an obvious secondary cause of osteoporosis or a fracture history may be more likely to request or be referred for bone density. In this regard, it is interesting that the proportion of women with fractures was higher in the women with IOP than in those with secondary osteoporosis (58% vs. 41%), although the difference was not significant.

The findings that lumbar spine BMD Z scores were significantly lower in the women with secondary osteoporosis but that forearm BMD was similar between the groups may reflect the fact that the most common causes identified in our study (premenopausal estrogen deficiency, glucocorticoids) predominantly affect cancellous bone, which is more abundant in the spine than at other sites. This finding, however, contrasts with the results of Peris et al.,⁹ who found lower femoral neck but similar lumbar spine Z scores in women with secondary osteoporosis. It should also be noted that although T and Z scores were quite similar in the groups with a mean age of 33–37 years, the women with IOP and no fractures (mean age 45 ± 4 years) had Z scores that appeared more “normal” than their T scores. As the Z score is a comparison to an age-matched reference group, women in their 40s may be compared to a reference population that includes some women who are already postmenopausal or who may have already started to lose bone mass.¹⁰

Mean heights and weights were lowest in those with low BMD and no history of fracture. On average, those with low BMD alone were 4.3 cm (or 1.7 inch) shorter and weighed considerably less (3.6 kg or 7.9 lb) than those with fractures. However, heights and weights were quite variable, and the overall differences between the groups were not statistically significant. DXA provides a 2-dimensional measurement of areal bone mineral content and density. Both are influenced by bone size, and, therefore, DXA may underestimate true mineral density in individuals with smaller skeletons.¹¹ Thus, it is entirely possible that true volumetric BMD may have been within the normal range for at least some of these women, particularly those of smaller stature. It is also possible, if not likely, that in some women, low BMD was due to having achieved low peak bone mass and that bone architecture, cancellous microarchitecture, connectivity, and strength are normal. In future, measurement of volumetric BMD and bone microstructure may be helpful in determining if women with low areal BMD by DXA truly have decreased volumetric BMD and bone strength.

A substantial number of the women in this report, 43%, had a history of current or past bisphosphonate therapy, 38% of the women with fractures and 47% of the women with low BMD alone. Given that one might expect physicians to treat women more aggressively if they have had fractures, it was notable that the women with low BMD only were just as likely to have been prescribed bisphosphonates as those with fractures. These observations are concerning and noteworthy, as bisphosphonates are not approved for use in premenopausal women unless the women are receiving glucocorticoids. Bisphosphonates have a very long elimination half-life and are labeled pregnancy category C due to toxic effects in pregnant rats.^{12,13} Data regarding safety of bis-

phosphonates in human pregnancies are sparse. There are several reports of normal pregnancy outcomes,^{14–16} but neonatal hypocalcemia and bilateral talipes equinovarus have been reported in offspring of 2 women with osteogenesis imperfecta.¹⁷

Since more studies have addressed epidemiology and treatment of osteoporosis in postmenopausal women and in men, premenopausal women with osteoporosis represent an understudied population with this condition. However, the diagnosis of osteoporosis in a premenopausal woman, particularly when based on fracture history, has implications for lifelong risk of fractures. A history of premenopausal fracture significantly increases the risk of a postmenopausal fracture.^{18–21} Data from the Study of Osteoporotic Fractures demonstrate that women with a history of premenopausal fracture are 35% more likely to fracture during the postmenopausal years than women without a history of premenopausal fracture.²⁰ This relationship persisted after controlling for a number of potential confounding variables. These findings suggest that the risk of sustaining fractures may be a lifelong trait, probably reflecting the interaction of an individual's bone mass, bone quality, fall frequency, and neuromuscular protective response to falls.¹⁸

The implications of the finding of low BMD in premenopausal women are less clear, especially in the absence of a known secondary cause. Although it has been reported that premenopausal women with distal forearm fractures have low ultradistal radius BMD,²² the predictive relationship between bone mass and fracture is orders of magnitude lower in premenopausal women than in postmenopausal women.^{23,24} Most premenopausal women are at very low short-term risk for fracture, regardless of BMD; thus, the fracture risk associated with low bone density in premenopausal women is likely to be low.

Relatively few evidence-based studies have addressed the appropriate management of premenopausal women with osteoporosis or low BMD. Because of the relatively low risk of fracture and also because of the issues surrounding pregnancy, most authorities in the field of osteoporosis do not recommend pharmacological therapy, particularly if there is no history of fracture and BMD is stable over a period of observation.^{5,6,23,25,26} In this regard, a small observational study of 16 premenopausal women with IOP followed for an average of 3 years, who were advised to increase calcium intake (to 1500 mg/day) and physical activity, found that BMD increased significantly at both the spine and femur and that there were no new fractures.²⁷ More aggressive treatment may be indicated in women who are taking glucocorticoids or who enter premature menopause during chemotherapy, those with one or more fractures, or those with ongoing bone loss. Because premenopausal fractures and low BMD predict postmenopausal fractures,^{18,20,28} one might also want to be more aggressive at the menopausal transition or in the older perimenopausal woman, in whom pregnancy is less of an issue.

This study has several limitations. Results were obtained from retrospective chart review rather than prospective study. The sample size of 61 was small, and the large number of comparisons conducted in this small number of patients increases the chance for type 1 error. Patients provided information on history of bisphosphonate use and calcium and vitamin D doses at the time of the initial visit, which may have led to reporting errors. The exclusion of secondary causes was based on studies ordered by different physicians

and performed in different commercial laboratories, and, thus, assignment to the idiopathic category could be inaccurate. Additionally, the group studied was a referral population seen at a tertiary care metabolic bone diseases program. This is very likely to have excluded women with more common or obvious secondary causes of osteoporosis and may create a bias toward a larger proportion of idiopathic cases.

Conclusions

In summary, we found that IOP is common among premenopausal women evaluated at a tertiary care medical center for low BMD or low-trauma fractures. The smaller stature of women diagnosed solely on the basis of BMD criteria raises the question of whether their areal BMD measurements were spuriously low because of their smaller bone size and suggests that a measurement of volumetric BMD may be useful to assess bone quality and strength in such individuals. The high proportion of premenopausal women who had been prescribed oral bisphosphonates is noteworthy. In particular, offering treatment with bisphosphonates solely on the basis of low BMD measurements is of concern, as such women are likely to be at low short-term risk of fracture. A more conservative approach to therapy is preferable in this group.

Disclosure Statement

No competing financial interests exist.

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